UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/779,376	02/07/2001	Jian-Bing Fan	A-68929-4/DJB/RMS/DCF	7981

7590 07/14/2004

Robin M. Silva, Esq.
FLEHR HOHBACH TEST ALBRITTON & HERBERT LLP
Suite 3400
Four Embarcadero Center
San Francisco, CA 94111-4187

EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/779,376	FAN ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,9-16,19-23,26 and 30-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,9-16,19-23,26 and 30-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *14 November 2002* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on February 23, 2004 has been entered. The claims pending in this application are claims 5, 9-16, 19-23, and 30-64. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn.

Claim Objections

2. Claim 59 is objected to because of the following informality: "said exogenous adapter sequence is nested between said first or second portions of said first ligation probe or said third or fourth portions of said second ligation probe" should be "said exogenous adapter sequence is nested between said first and second portions of said first ligation probe or said third and fourth portions of said second ligation probe".

Appropriate correction is required.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 5, 13, 32, 39, 45, and 57 are rejected under 35 U.S.C. 102(e) as being anticipated by Barany *et al.*, (US Patent No. 6,027,889, filed on May 28, 1997).

Barany *et al.*, teach detection of nucleic acid sequence differences using coupled ligase detection and polymerase chain reactions.

Regarding claims 5, 32, 39, and 57, as shown in Figures 12-17, a first oligonucleotide probe having a target-specific portion and a 5' upstream primer-specific portion, and a second oligonucleotide probe having a target-specific portion and a 3' downstream primer-specific portion are hybridized adjacent to one another on a corresponding target nucleotide sequence and are ligated together in a ligase chain reaction. However, if there is a mismatch in ligation end of the first or second probe, this mismatch will interfere with such ligation. Then unligated the first probe and the second probe are removed with Exo I and PCR-amplified using an upstream primer containing the same sequence as the 5' upstream primer-specific portion of the ligation product sequence (in the first probe) and a downstream primer complementary to the 3' downstream primer-specific portion of the ligation product sequence (in the second probe) wherein one primer has a detectable reporter label. Finally, PCR products are hybridized with a DNA array with different capture oligonucleotides immobilized at different particular sites and have nucleotide sequences complementary to the unique nucleotide sequences across the ligation junctions of given probe sets, and the labels of the PCR products captured on the DNA array at particular sites are detected as recited in steps f) and g) of claims 5, 32, 39, and 57 (see Figures 12-17 and columns 9, 10, 25-28, and 79-90). Note that: (1) the specification defines "universal priming site" as " a sequence of the probe that will bind a PCR primer for amplification" (see

page 13, lines 14 and 15), the first probe and second probe are considered as first probe with the first and second portions and second ligation probe with the third fourth, and fifth portions as recited in claims 5, 32, 39, and 57 (see attached Figure 12 with the examiner's handwritings); (2) since claims 5, 32, 39, and 57 do not require that step c) must perform before step d), Exo I digestion step in Figure 12 is considered as step c) recited in claims 5, 32, 39, and 57; (4) as shown in Figure 12, base G in left probe (a first ligation probe) that hybridizes to mutant sequence is considered as a first base at an interrogation position as recited in claim 5 and 39 or an interrogation position that is complementary to said detection position in a first ligation probe as recited in claim 32 and 57; and (5) according to the definition of "adaptor sequence" (see page 19, third paragraph), the fifth portion of the second ligation probe (see attached Figure 12 with the examiner's handwritings) is considered to have an exogenous adaptor sequence as recited in claims 39 and 57 because the second ligation probe is synthesized *in vitro* and artificially made, and is exogenous to the target sequence.

Regarding claims 13 and 45, since Barany *et al.*, teach to amplify the ligation product by PCR and basic PCR steps include repeated denaturation, annealing and extension, Barany *et al.*, disclose claims 13 and 45.

Therefore, Barany *et al.*, teach all limitations recited in claims 5, 13, 32, 39, 45, and 57.

Response to Arguments

In page 16, last paragraph bridging to page 18, third paragraph of applicant remarks, applicant argues that: (1) "[T]he Examiner appears to assert that the UUP portion or the DUP portion of the claimed probes can include both a UUP or a DUP and an adaptor portion.

Applicants contend that this interpretation is unfound, especially in light of the recitation of portions 1-5 in the ligation probes of the invention. The claims specify different elements within the probes and a correspondence to different portions within the probes."; and (2) "Because Barany et al. purportedly describes adaptors that correspond specifically to target sequences that correspond to 'a nucleotide sequence across the ligation junction' and the claimed adaptors correspond to fifth portion of a probe differing from the second and fourth target specific sequence, the probe configuration of Barany et al. teaches away from the adaptors as currently claimed".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, Barany *et al.,* do teach the first, second, third, fourth, and fifth portion wherein the fifth portion is distinct from said first, second, third, or fourth portion (see attached Figure 12 with the examiner's handwritings). Second, claims 5, 32, 39, and 57 do not require that the adaptor sequence is a sequence that corresponds specifically to target sequences that corresponds to a nucleotide sequence across the ligation junction as suggested by applicant. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 14-16, 34, 46-48, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany *et al.*, (1997) as applied to claims 5, 13, and 32 above, and further in view of Walt *et al.*, (US Patent No. 6,327,410 B1, filed on September 11, 1998).

The teachings of Barany *et al.*, have been summarized previously, *supra.*

Barany *et al.*, do not disclose an array recited in claims 14-16, 34, 46-48, and 60.

Walt *et al.*, do teach an array comprising a substrate such as a fiber optical bundle recited in claims 16, 34, 48, and 60 with a patterned surface with discrete sites such as wells recited in claims 15 and 47, and a population of microspheres comprising at least a first subpopulation and a second subpopulation wherein said first subpopulation comprises a first nucleic acid and second subpopulation comprises a second nucleic acid, and wherein said microspheres are randomly distributed on said surface such that said discrete sites contain microspheres recited in claims 14 and 46 (see Figures 7A and 7B, columns 3, 4, and 28-30).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claims 5 and 32 using an array recited in claims 14-16 and 34 in view of the patents of Barany *et al.,* and Walt *et al.*. One having ordinary skill in the art would have been motivated to modify the method of Barany *et al.,* because the simple replacement of one kind of nucleic acid array (a regular oligonucleotide array) from another kind of nucleic acid array (an array with microspheres having immobilized nucleic acids) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement of one kind of nucleic acid array from another kind of nucleic acid array during the process of determining the identification of a nucleotide at a detection position in a target sequence would not change the method steps of the experiment.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 18, last paragraph bridging to page 20, first paragraph of applicant's remarks, applicant argues that "[A]pplicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness, at least because all the components of the claimed ligation probes are not taught or suggested by the cited art. The pending claims recite ligation probes containing a fifth portion, distinct from target-specific portions or UUP or DUP portions, or where the fifth portion corresponds to an exogenous sequence. However, the cited references, alone or in combination, at least do not teach or suggest a ligation probe containing these elements. For example, Barany et al. purports to describe an adaptor oligonucleotide that corresponds to a nucleotide sequence across the ligation junction. Because the ligation junction corresponds to a target-specific sequence, the purported description of Barany et al. do not teach or suggest an adaptor portion distinct from other portions as claimed. In the absence of a teaching or suggestion in the cited references of each of the components of the claimed ligation probes, the Office has not established a *prima facie* case of obviousness of any of the claims under 35 U.S.C. § 103(a).".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Since Barany *et al.,* teach the first, second, third, fourth, and fifth portion wherein the fifth portion is distinct from said first, second, third, or fourth portion (see attached Figure 12 with the examiner's handwritings), Barany *et al.,* disclose all the components of the claimed ligation probes. Therefore, the Office has not established a *prima facie* case of obviousness of claims 14-16, 34, 46-48, and 60 under 35 U.S.C. § 103(a)

7. Claims 10, 13, 19-22, 26, 31, 33, 35, 42, 45, 49-52, 54, 56, 58, 59, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.,* (US Patent No. 5,876,924, filed on July 31, 1996) in view of Barany *et al.,* (1997).

Regarding claims 10, 13, 19-22, 26, 31, 33, and 35, Zhang *et al.,* teach nucleic acid amplification method hybridization signal amplification method. As shown in Figures 1 and 2, the two oligonucleotide probes (Capture/Amp-probe-1 and Amp-probe-2) are first hybridized adjacent to one another on a corresponding target nucleotide sequence of the target nucleic acid in a sample wherein the Capture/Amp-probe-1 is 3'-biotinylated. Then the complex comprising target nucleic acid-probes is separated from any unbound reactants using streptavidin-coated paramagnetic beads as recited in claims 10, 19, 20, 31, 42, 49, 50, and 56 and the probes is ligated together in a ligation chain reaction. Ligated product of Capture/Amp-probe-1 and Amp-probe-2 are used as a template for PCR (see Figures 1 and 2, and columns 10-17). This method is used to detect a single mutation in a target (see column 6, first paragraph). Note that: (1) since claims 26, 33, 54, and 58 do not require that step a) must perform before step b), binding of target nucleic acid-probe complex to streptavidin-coated paramagnetic beads is considered to provide a support on which the target sequence is immobilized recited in step a) of claims 26, 33, 54, and 58; (2) Capture/Amp-probe-1 is considered to have a first portion and a second portion while AMP-PROBE-2 is considered to have third portion, fourth portion, and fifth portion (see attached Figure 1 with examiner's handwritings) wherein said exogenous adapter sequence is nested between said third and fourth portions of said second ligation probe as recited in claim 59; (3) streptavidin-coated paramagnetic beads are considered as a double-

stranded moiety as recited in claims 10 and 42 since they bind to and separate the complex comprising target nucleic acid-probes which is double stranded from any unbound reactants; (4) the target nucleic acid is considered to be indirectly immobilized on streptavidin-coated paramagnetic beads as recited in claims 19, 21, 49, and 51; (5) biotinylated Capture/Amp-probe-1 is considered as a functional attachment moiety recited in claims 22 and 52 since this probe attaches the target nucleic acid to streptavidin-coated paramagnetic beads in the target nucleic acid-probe complex; and (6) a base located in 5' of capture/AMP-probe is considered as an interrogation position as recited in claims 26, 33, 54, and 58 (see Figure 1).

Zhang *et al.*, do not disclose steps g) and h) of claims 26, 33, 54, and 58.

The teachings of Barany *et al.*, have been summarized previously, *supra.* Barany *et al.*, also teach steps g) and h) of claims 26, 33, 54, and 58 (see above).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claims 26 and 33 using a PCR product made by Zhang *et al.*, as a hybridization probe in view of the patents of Barany *et al.*, and Zhang *et al.*. One having ordinary skill in the art would have been motivated to do so because the simple replacement of one well known LDR/PCR method (LDR/PCR method of Barany *et al.*,) from another well known LDR/PCR method (LDR/PCR method of Zhang *et al.*,) in order to make a hybridization probe would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to make a hybridization probe would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 20, second paragraph bridging to page 21, last paragraph of applicant's remarks, applicant argued that: (1) "[S]ince neither Zhang nor Barany teach or suggest hybridization of probes to a target, wherein the probes include the five portions outlined herein, the requirement that the prior art reference (or references when combined) must teach or suggest all the claim limitations has not been met."; and (2) "there is lacking any motivation to modify or combine reference teachings. First of all contrary to the Examiner's characterization of Zhang as an LDR process like Barany, they operate in distinctly different ways. The LDR process of Barany uses hybridization probes directed to extension products (amplified products). In contrast, Zhang is directed to methods where the target is first captured through the use of capture probes and paramagnetic beads, then ligation occurs while still attached to the beads and after there is a release of the ligated amplification sequence from the beads, then there is amplification using a suitable PCR technique. See Zhang et al. at column 15, lines 35-41. lf the proposed modification or combination of the prior art would change the principle operation of the prior art being

modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 19S9)"; and (3) "[T]he combination of the references would require substantial reconstruction and redesign of the elements shown in the primary reference (Zhang et al.) as well as a change in the basic principle under which Zhang et al. was designed to operate".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, Zhang *et al.,* do teach a ligation probe comprising a first portion and a second portion or a third portion, a fourth portion, and fifth portion (see attached Figure with the examiner's handwritings). Second, although this rejection is based on modifying the method of Zhang *et al.*. However, modification would not alter the principle operation because the rejection is based on that the simple replacement of one well known LDR/PCR method (LDR/PCR method of Barany *et al.,*) from another well known LDR/PCR method (LDR/PCR method of Zhang *et al.,*) in order to make a hybridization probe would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to make a hybridization probe would not change the experimental results (see M.P.E.P. at 2144.06, 2144.07 and 2144.09).

8. Claims 11, 12, 43, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.,* (1996) in view of Barany *et al.,* (1997) as applied to claims 10, 13, 19-22, 26, 31,

33, 35, 42, 45, 49-52, 54, 56, 58, 59, and 61, and further in view of Gebeyehu *et al.*, (US Patent No. 4,921,805, published on May 1, 1990).

The teachings of Zhang *et al.*, and Barany *et al.*, have been summarized previously, *supra.*

Zhang *et al.*, and Barany *et al.*, do not disclose that said double-stranded specific moiety is an intercalator attached to a support wherein said support is a bead as recited in claims 11, 12, 43, and 44.

Gebeyehu *et al.*, teach to use an intercalator attached to a bead to separate non-hybridized probes from hybridized probes (see column 3, lines 39-54 and claims 1-10 in columns 12-14).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have removed non-hybridized probes using a method recited in claims 11, 12, 43, and 44 in view of the prior art of Barany *et al.*, Zhang *et al.*, and Gebeyehu *et al.*. One having ordinary skill in the art would have been motivated to do so because Gebeyehu *et al.*, have successfully separated non-hybridized probes from hybridized probes using an intercalator attached to a bead and the simple replacement of one well known nucleic acid separation method (based on the interaction between a ligand on a target nucleic acid with its binding partner) from another well known nucleic acid separation method (based on the interaction between a double nucleic acid probe with an intercalator) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one

having ordinary skill in the art at the time the invention was made since using different methods to remove non-hybridized probes would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

9. Claims 9, 23, 30, 41, 53, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.*, (1996) in view of Barany *et al.*, (1997) as applied to claims 10, 13, 19-22, 26, 31, 33, 35, 42, 45, 49-52, 54, 56, 58, 59, and 61, and further in view of Seradyn Particle Technology (November 1996).

The teachings of Zhang *et al.*, and Barany *et al.*, have been summarized previously, *supra.*

Seradyn Particle Technology (page 7) confirms that streptavidin-coated paramagnetic beads taught by Zhang *et al.*, comprise a plastic material as recited in claims 23,30, 53, and 55 since these beads has polystyrene core.

Zhang *et al.*, Barany *et al.*, and Seradyn Particle Technology do not disclose claims 9 and 41 wherein the target sequence is labeled with a binding ligand. However, Zhang *et al.*, teach

steps b) to d) in claims 9 and 41 except the probe is labeled with a binding ligand in step a) (see column 8 and 10-13).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have removed non-hybridized probes using a method recited in claim 9 or 41 in view of the prior art of Barany *et al.*, Zhang *et al.*, and Seradyn Particle Technology. One having ordinary skill in the art would have been motivated to do so because a method for labeling different nucleic acids with a binding ligand was known in the art at the time the invention was made and the simple replacement of one well known nucleic acid separation method (based on the interaction between a ligand on a target nucleic acid with its binding partner) from another well known nucleic acid separation method (based on the interaction between a ligand on a nucleic acid probe with its binding partner) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to remove non-hybridized probes would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

10. Claim 37 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.*, (1996) in view of Barany *et al.*, (1997) as applied to claims 10, 13, 19-22, 26, 31, 33, 35, 42, 45, 49-52, 54, 56, 58, 59, and 61 above, and further in view of Monforte *et al.*, (US Patent No. 5,830,655, published on November 3, 1998).

The teachings of Zhang *et al.*, and Barany *et al.*, have been summarized previously, *supra.*

Zhang *et al.*, and Barany *et al.*, do not disclose that said target sequence is attached to said support by direct chemical attachment of said target sequence to said support as recited in claims 37 and 63.

Monforte *et al.*, teach to immobilize nucleic acid templates by attachment to a solid support before a primer extension assay. Immobilization was via a covalent or non-covalent linkage (see last paragraph of column 6 and claims 1-3 in column 63).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 37 or 63 by attaching target sequences taught by Zhang *et al.*, onto a solid support in view of the patent of Monforte *et al.*. One having ordinary skill in the art would have been motivated to do so because Monforte *et al..*, have successfully attached nucleic acid templates to a solid support before

amplification of the nucleic acid templates and the immobilization of the nucleic acid templates to a solid support would enhance to separate hybridized complexes formed by the nucleic acid templates and hybridized probes from unhybridized probes and the simple replacement of one well known nucleic acid separation method (based on the interaction between a ligand on a target nucleic acid with its binding partner that immobilizes on a solid support taught by Zhang *et al.*,) from another well known nucleic acid separation method (based on the interaction between ligation probes with target sequences immobilized on a solid support) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to remove non-hybridized probes would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

11. Claims 36 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.*, (1996) in view of Barany *et al.*, (1997) and further in view of Monforte *et al.*, (1998) as

applied to claims 10, 13, 19-22, 26, 31, 33, 35, 37, 42, 45, 49-52, 54, 56, 58, 59, 61, and 63 above, and further in view of Brown *et al.*, (US Patent No. 5,807,522, published on September 15, 1998).

The teachings of Zhang *et al.*, Barany *et al.*, and Monforte *et al.*, have been summarized previously, *supra.*

Zhang *et al.*, Barany *et al.*, and Monforte *et al.*, do not teach that said target sequence is attached to said support by absorption of said target sequence on said support wherein said support comprises charged groups as recited in claims 36 and 62.

Brown *et al.*, teach to immobilize nucleic acids onto a support comprising charged groups (ie., a slide with a layer of poly-l-lysine) (see column 16).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 36 or 62 by attaching target sequences taught by Zhang *et al.*, onto a solid support comprising charged groups in view of the patents of Monforte *et al.*, and Brown *et al.*. One having ordinary skill in the art would have been motivated to do so because, due to interaction between negative charges of the nucleic acids and positive charges of the support, immobilization of nucleic acids onto a solid support comprising positive charged groups would increase efficiency of the immobilization and the simple replacement of one solid support (ie., the support taught by Monforte *et al.*.) from another solid support (ie., the support with positive charges taught by Brown *et al.*) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the

contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to remove non-hybridized probes would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

12. Claims 38 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.*, (1996) in view of Barany *et al.*, (1997) and further in view of Monforte *et al.*, (1998) as applied to claims 10, 13, 19-22, 26, 31, 33, 35, 37, 42, 45, 49-52, 54, 56, 58, 59, 61, and 63 above, and further in view of Johnson *et al.*, (US Patent No. 6,372, 813, published on June 25, 1999).

The teachings of Zhang *et al.*, Barany *et al.*, and Monforte *et al.*, have been summarized previously, *supra.*

Zhang *et al.*, Barany *et al.*, and Monforte *et al.*, do not teach that said target sequence is attached to said support by photocrosslinking said target sequence to said support as recited in claim 36.

Johnson *et al.*, teach to photocrosslink a nucleic acid onto a solid support (see example 5, column 21).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 38 or 64 by attaching target sequences taught by Zhang *et al.*, onto a solid support by photocrosslinking in view of the patents of Monforte *et al.*, and Johnson *et al.*. One having ordinary skill in the art would have been motivated to do so because Johnson *et al.*., have successfully photocrosslinked a nucleic acid onto a solid support and the simple replacement of one well known nucleic acid immobilization method (an immobilization method taught by Monforte *et al.*,) from another well known nucleic acid immobilization method (an immobilization method taught by Johnson *et al.*,) during the process of determining the identification of a nucleotide at a detection position in a target sequence would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since using different methods to remove non-hybridized probes would not change the experimental results.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 22 of applicant's remarks, applicant argues that "[C]laims 9, 23, 30, 36 and 37 all depend from one or more of the independent claims 5, 26, 32 and 33. Accordingly, the dependent claims contain all the limitations of the base claims from which they depend. As set fourth above, neither Barany et al. in view of Walt nor Zhang et al. in view of Barany et al. provide all the elements of the claimed invention or a motivation to combine the respective references. Accordingly, the independent claims are unobvious over the cited combination of references. The above tertiary references are cited allegedly for describing a further element found within the dependent claims. Because the cited art fails to describe each and every element of the claimed invention and because the tertiary references are directed to further elements within the dependent claims, the citations to Seradyn Particle Technology, Monforte et al. or Johnson et al. cannot cure the deficiencies of the primary and secondary references. Accordingly, the cited art to claims 9, 23, 30, 36 and 37 cannot teach or suggest each and every element of the claimed invention".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection because Zhang *et al.,* do teach a ligation probe comprising a first portion and a second portion or a third portion, a fourth portion, and fifth portion (see attached Figure with the examiner's handwritings).

Conclusion

13. No claim is allowed.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
June 28, 2004

FRANK LU
PATENT EXAMINER